REMARKS

Status of and Amendments to the Claims

In the Office Action dated February 24, 2004 it was noted that claims 75-77 and 81-83 were withdrawn as allegedly reading on non-elected inventions. Applicants thank the Examiner for reconsidering his position on this matter in the interview with the undersigned on April 21, 2004. Claims 75-77 and 81-83 are amended herein for clarity, as suggested by the Examiner.

Claims 92-94 are canceled herein to expedite prosecution of this application. Please note that Applicants reserve the right to file divisional or continuation applications claiming the canceled subject matter, and that the claim cancellations should not be construed as abandonment of the claimed subject matter or agreement with any objection or rejection of record.

Claims 68-69, 75-77, 81-83, 86-91 and 103-105 are pending with entry of this amendment. Claims 106-112 are currently withdrawn from consideration as being directed to non-elected methods. In the interview on April 21 the Examiner noted his willingness to rejoin these claims upon a finding of allowablity of the product claims from which they depend, in accordance with MPEP §821.04.

Previous Rejection under 35 USC §112 paragraph 1

In the Office Action dated August 12, 2003, claim 68 was rejected under 35 USC §112 paragraph 1 for allegedly failing to comply with the Written Description requirement.

The Examiner's consideration of remarks make in the amendment dated December 10, 2003 and withdrawal of the rejection in the Office Action dated February 24, 2004 is noted with appreciation.

Previous Objection to the Claims and Specification

In the Office Action dated August 12, 2003, it was noted that "The specification and claims are objected to for failing to adhere to the requirements of the sequence rules. Applicant must append SEQ ID NO's to all mentions of specific sequences in the specification and the claims. See 37 CFR 1.821(d)".

Applicants responded to these objections in the amendment dated December 10, 2003.

The Office Action dated February 24, 2004 provides no indication of the status of these objections. Applicants would appreciate clarification of this matter in the next Official Action.

Information Disclosure Statement

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Supplemental IDS originally submitted on July 1, 2002, as evidenced by the initialed and signed copy of the one-page Form 1449 citing four references (numbered 1-4) included with the Office Action dated February 24, 2004.

Rejection under 35 USC §103(a)

The Examiner maintained the rejection of claims 68-69, 86-89, 91, 93-94, and 103-105 under 35 USC § 103(a) as allegedly being unpatentable over US Patent 5,861,374 issued to Berkner *et al.* (hereinafter "Berkner"). Claims 93 and 94 are canceled herein to expedite prosecution of the instant application, rendering the rejection of these claims moot. Applicants respectfully traverse the rejection of the remaining claims, for the following reasons.

In maintaining the rejection, it was stated:

> ....Applicant contends that the examiner's office action does not point with any particularity to any teaching or suggestion in Berkner (USPN 5,861,374) which would motivate one of skill to make a conjugate comprising a polypeptide comprising an amino acid sequence which differs from the hFVII or hFVIIa sequence SEQ ID NO:1 in 1-15 amino acid residues. (Office Action, page 3, lines 2-5)

Applicants' invention, as embodied in claim 68, is directed to conjugate comprising a polypeptide comprising an amino acid sequence which differs from the hFVII or hFVIIa sequence SEQ ID NO:1 in 1-15 amino acid residues and comprises an introduced *in vivo* N-glycosylation site relative to SEQ ID NO:1, wherein the introduced *in vivo* N-glycosylation site comprises the substitution T106N; and a sugar moiety covalently attached to the introduced *in vivo* N-glycosylation site, wherein the conjugate exhibits at least 25% of the clotting activity of hFVIIa. All of the other claims pending in this application incorporate these elements by virtue of their dependence from claim 68.

Three requirements must be met to establish a *prima facie* case of obviousness:

1. The Office Action must demonstrate how the prior art reference teaches or suggests all of the limitations of the rejected claims. MPEP §2143.03.

2. The Office Action must point to a particular suggestion or motivation provided either in the cited reference or in the knowledge generally available to one of ordinary skill in the art, to modify the reference to produce the claimed invention. MPEP § 2143.01.

3. The Office Action must demonstrate a reasonable expectation of success of carrying out the claimed invention based on the teachings of the cited reference. MPEP §2143.02.

Furthermore, the teaching or suggestion to modify the cited reference, and the reasonable expectation of success, must both be found in the cited reference and not based on Applicants' disclosure. MPEP §2143.

The deficiencies of the Office Action in meeting each of these criteria is discussed below.

1. The Office Action has not established with any particularity how the Brukner reference teaches or suggests each and every element of independent claim 68, or any claim dependent thereon.

In making the rejection, it was stated:

> ... The examiner contends that Berkner teaches pharmaceutical compositions of modified factor VII that are used to treat a variety of coagulation-related disorders, see abstract. Berkner discloses SEQ ID NO:2, which has a 99.1% query match with SEQ ID NO:1 of the instant application. This query match differs by 4 amino acids from the claimed instant sequence. The instant specification recites "In order to avoid too much disruption of the structure and function of the parent molecule the polypeptide part of the conjugate will typically have an amino acid sequence having more than 90% identity with SEQ ID NO:1, preferably more than 95%, such as more than 96%. In particular, the polypeptide part of the conjugate will typically have an amino acid sequence having more than 97% identity with SEQ ID NO:1, such as more than 98%, more than 99%..." see page 18, lines 30-35. *(Office Action, page 3)*

Applicants do not dispute the above statements; however, these statements do not address how the cited reference teaches or suggests each and every element of the claimed invention. Several elements of pending claim 68, and claims which depend thereon, are not addressed in the rejection. Specifically, the Office Action does not point to any teaching or suggestion in the

cited reference to introduce an *in vivo* N-glycosylation site into SEQ ID NO:1 (or into SEQ ID NO:2 disclosed in Berkner), as is recited in claim 68 and claims which depend thereon. More specifically, the Office Action does not point to any teaching or suggestion in the cited reference to introduce a T106N substitution into SEQ ID NO:1 (or into SEQ ID NO:2 disclosed in Berkner) as is recited in claim 68 and claims which depend thereon. Furthermore, the Office Action does not point to any teaching or suggestion in the cited reference to produce a conjugate containing a sugar moiety covalently attached to an introduced *in vivo* N-glycosylation site, wherein the conjugate exhibits at least 25% of the clotting activity of hFVIIa, as is recited in claim 68 and claims which depend thereon.

In light of the above, Applicants respectfully submit that the rejection has not demonstrate how the cited reference teaches or suggests all of the limitations of the rejected claims, and thus does not fulfill the first requirement of a *prima facie* case of obviousness listed above.

2. The Office Action does not point to a particular suggestion or motivation, provided either in the cited reference or in the knowledge generally available to one of ordinary skill in the art, to modify the reference to produce the invention as claimed in independent claim 68 or any claim dependent thereon.

Applicants submit that Office Action does not point to any teaching or suggestion in Berkner which would motivate one of skill to make a conjugate comprising a polypeptide comprising an amino acid sequence which differs from the hFVII or hFVIIa sequence SEQ ID NO:1 in 1-15 amino acid residues and which comprises an introduced *in vivo* N-glycosylation site relative to SEQ ID NO:1, wherein the introduced *in vivo* N-glycosylation site comprises the substitution T106N; and a sugar moiety covalently attached to the introduced *in vivo* N-glycosylation site, wherein the conjugate exhibits at least 25% of the clotting activity of hFVIIa, as recited in claim 68 and claims which depend thereon. The Office Action does not articulate any line of reasoning which would explain, when provided with the Berkner reference (and SEQ ID NO:2 therein), how one of skill would be motivated to modify a FVII sequence to introduce any *in vivo* N-glycosylation site into the sequence. Moreover, the Office Action does not

articulate any line of reasoning which would explain how one of skill, when provided with the Berkner reference (and SEQ ID NO:2 therein), would be motivated to introduce the particular claimed *in vivo* N-glycosylation site, via the substitution T106N, into SEQ ID NO:2 or into any other FVII sequence. Inspection of SEQ ID NO:2 disclosed in Berkner shows that position 106 in that sequence is a Thr. The Office Action does not point to any teaching or suggestion in Berkner which would motivate one of skill to modify that Thr (T) at that position 106 to an Asn (N). The Office Action furthermore does not point to any teaching or suggestion in Berkner which would motivate one of skill to covalently attach a sugar moiety to an introduced *in vivo* N-glycosylation site, such as the *in vivo* N-glycosylation site introduced by way of the substitution T106N. As noted above, such motivation must originate from the cited reference(s), not from Applicants' own disclosure. A suggestion to modify the cited reference to arrive at the claimed invention cannot simply be assumed without support for such modification in the cited reference.

In light of the above, Applicants respectfully submit that the rejection has not demonstrated how one of skill, when provided with the cited reference, would be motivated to modify the cited reference to produce the invention as claimed in independent claim 68 or any claim dependent thereon, and thus does not fulfill the second requirement of a *prima facie* case of obviousness.

3. The Office Action had not demonstrated a reasonable expectation of success, based on the teachings of the cited reference, in carrying out the invention as claimed in independent claim 68 or any claim dependent thereon.

Applicants respectfully submit that the Office Action does not point to any teaching or suggestion in the cited art which would provide one of skill a reasonable expectation that, based on the teachings of cited art, the invention as claimed in independent claim 68 or any claim dependent thereon would be successful. In particular, the Office Action points to no teaching or suggestion in Berkner which would provide one of skill a reasonable expectation that introduction of an *in vivo* N-glycosylation site into SEQ ID NO:1, and covalent attachment of a sugar moiety to the introduced *in vivo* N-glycosylation site, would result in a conjugate which exhibits at least 25% of the clotting activity of hFVIIa.

On the contrary, Berkner describes modified FVIIa molecules with "substantially inhibited" activity. According to Berkner at col 5 lines 48-52:

> For the modified Factor VII the catalytic activity will be substantially inhibited, generally less than about 5% of the catalytic activity of wild-type Factor VII of the corresponding species, more preferably less than about 1% (emphasis added).

Example II of Berkner describes production of modified Factor VII proteins which exhibit no detectable coagulant activity (see col. 14, lines 17-18). It is difficult to envision how the Berkner reference would provide one of skill a reasonable expectation of successfully preparing the claimed conjugate, exhibiting at least 25% of the clotting activity of hFVIIa, when the Berkner reference itself teaches the preparation of modified FVII molecules with "generally less than less than about 5% of the catalytic activity of wild-type Factor VII of the corresponding species", and exemplifies production of modified Factor VII molecules with "no detectable coagulation activity".

In light of the above, Applicants respectfully submit that the Office Action has not sufficiently demonstrated any reasonable expectation of success in making the invention as claimed in independent claim 68 or any claim dependent thereon based on the teachings of Berkner. Therefore, the rejection does not fulfill third requirement of a *prima facie* case of obviousness.

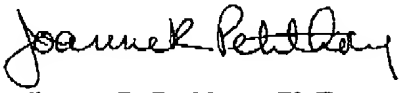
For at least the reasons provided above, Applicants respectfully submit that none of the three requirements for a *prima facie* case of obviousness have been met in the rejection of pending claims 68-69, 86-89, 91, and 103-105 under 35 USC § 103(a) as allegedly unpatentable over Berkner. Applicants respectfully request the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe the claims pending in this application are in condition for allowance. Early notification to that effect is earnestly solicited.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 298-5452.

Respectfully submitted,



Joanne R. Petithory, Ph.D.
Reg. No. 42,995

Maxygen, Inc.
Intellectual Property Dept.
515 Galveston Drive
Redwood City, CA 94063
Customer Number 30560

Phone: (650) 298-5452 (direct)
(650) 298-5300 (main)
Fax: (650) 298-5446

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